DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 2 6 2000

Mr. Thomas Craig
President
Orthopaedic Surgical Manufacturers Association
1962 Deep Valley Cove
Germantown, Tennessee 38138

Re: Reclassification 21CFR888.3320 and 21CFR888.3330
Metal/Metal Semi-Constrained Hip Joint Prosthesis with Cemented and Uncemented Acetabular Components
Filed: December 1, 2000

Dear Mr. Craig

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced reclassification petition. We regret to inform you that on the basis of this review, we have concluded that the petition lacks information needed to determine whether all the risks associated with the device have been identified and how these risks may be controlled for the purposes of reclassification.

To complete the review of your petition , we request the following additional information:

1. The disclosure of compensation and financial information is applicable to this reclassification petition. Applicants must certify to the absence of certain financial interests of clinical investigators on Financial Interest Form: Certification: Financial Interests and Arrangements of Clinical Investigators FDA Form 3454 (http://forms.psc.gov/forms/FDA/fda3454.pdf) or to disclose those financial interests on Financial Interest Forms: Disclosure: Financial Interests and Arrangements of Clinical Investigators FDA Form 3455 (http://forms.psc.gov/forms/FDA/fda3455.pdf).

   The information that must be disclosed include the following:

   - Compensation made to the investigator in which the value of the compensation could be affected by the study outcome.

   - Significant payments to the investigator or institution with a monetary value of $25,000 or more (e.g. grants, equipment, retainers for ongoing consolation, or honoraria) over the cost of conducting the trial. Any such payments to the investigator or institution during the time the investigator is conducting the study and for one year following study completion, must be reported.

   - Proprietary interest in the device, such as a patent, trademark, copyright, or licensing agreement.

- Significant equity interest in the sponsor such as ownership, interest, or stock options. All such interests whose value cannot be readily determined through reference to public prices must be reported. If the sponsor is a publicly traded company, any equity interest whose value is greater than $50,000 must be reported. Any such interests held by the investigator while the investigator was conducting the study and for one year following study completion must be reported.

Please provide the financial disclosure information for the four clinical studies conducted in the United States and included in the reclassification petition.

2. In your reclassification petition you have described four unpublished clinical studies (Study A, B, C, and D). The following deficiencies relate to those four studies:

a. You have presented clinical data from four non-published studies, but you have not provided a complete summary of the timecourse distributions of the clinical data or patient accounting information (e.g. Harris Hip Score levels: Excellent, Good , Fair, and Poor) over the course of each study (e.g. pre-op, post-op, 6 months, 12 months, 24 months). This information would allow us to adequately analyze primary clinical endpoints and patient accountability information for each unpublished clinical study. Please provide timecourse distribution of the clinical data and patient accountability information for Study A, Study B, Study C, and Study D. The enclosed guidance "General ORDB Outline for Clinical Data Presentation in Premarket Notifications (510(k)) Submissions, Investigational Device Exemptions (IDE) Annual Reports, or Premarket Approval (PMA) Applications" dated June 1991, should be used as a guide for formatting these data.

b. You have not provided complete radiographic data for the patients in the four unpublished clinical studies. For example, in Studies A, B, C you did not provide any radiographic data on acetabular cup migration, radiolucencies, or other signs of acetabular loosening. In addition, there was no radiographic information on the presence of heterotopic ossification. In Study D, you did not provide any radiographic data. Although Study D contained clinical data, radiographs provide essential information, including early signs of loosening. Please provide complete radiographic data from all four unpublished clinical studies including acetabular cup migration, radiolucencies, or other signs of acetabular loosening. If radiographic data are not available for Study D, please explain why this information is unavailable.

c. When describing each device used in each unpublished clinical study, you provided a picture of the device and device materials, but did not provide the name and specifications of the device (e.g. femoral head size, acetabular cup size, type of cup). Please provide the specific name of the device and specific sizes and measurements of each device used in Study A, Study B, Study C, and Study D.

d. Please provide the investigational protocols for Study A, Study B, Study C, and Study D.

e. In each study, you compared the data from metal/metal hip joint prostheses to data from metal/polyethylene hip joint prostheses by providing only the means of various clinical endpoints. Please provide an analysis of the results for each study based on the analysis in the study protocol. Additionally, please describe the criteria for individual patient success, based on clinical and radiographic parameters, and provide a comparison of the results of the studies individually, if this type of analysis was not described in the protocol. Please provide an analysis of the pooled study results looking at individual patient success as well. In your analysis, the time after surgery at which an assessment for effectiveness was made needs to be taken into account.

f. For some of the clinical studies you provided the number of revisions and removals of the device in Study A, B, D but did not provide this data for Study C. Please provide the number of revisions, reoperations, and removals for all of the unpublished clinical studies.

3. In your reclassification petition, you have provided a list of proposed test methods that are intended to control specific risks. In order to control the risks associated with metal/metal wear, you proposed the use of hip simulator testing. Because there are many different types of hip simulators and test protocols that produce varying results, please identify important issues to consider when conducting and evaluating hip simulator testing. Please describe the test methods that would predict clinical wear and the evidence supporting the use of those methods in order to show the risk can be addressed with this special control.

4. In the reclassification petition, you have identified geometry and surface finish of the femoral head and acetabular component as two important design considerations for a metal/metal semi-constrained hip joint prosthesis but did not provide any specific values. Some of these features such as sphericity, clearance, and surface roughness play an important role in the success of a metal/metal hip prosthesis. Please provide a table of values for the sphericity, clearance, and surface roughness for each metal/metal semi-constrained hip joint prosthesis identified in the published literature and unpublished clinical data contained in this petition.

5. In the reclassification petition, you have provided a summary of different published literature articles on clinical studies performed using metal/metal hip joint prosthesis. The following deficiencies relate to the published clinical data:

a. In Tables 8 and 9 of the petition, titled "Clinical Outcomes of Published Literature" and "Adverse Effects of Published Literature", you have provided

follow-up, pre-op score, post-op score, and several other categories for analyzing the published literature. However, you have not provided copies of the literature articles upon your summaries were based. Therefore, please provide copies of all literature articles cited in Tables 8 and 9.

b. In the reclassification petition, you have summarized several published articles but you have not identified how your literature search was performed including:

- Name(s) of the databases;
- Search terms (i.e. keywords);
- Range of years; or
- Acceptance and rejection criteria for each journal article.

Therefore, in order to insure that you have performed a complete search to fully characterize the risks associated with metal/metal prosthesis, please provide this information in your next submission.

6. In your reclassification petition, you have identified only one medical device report (MDR) between January 1, 1992 and June 29, 2000. Because the reclassification petition contains both pre-amendments and recently cleared devices, please review all MDRs for metal/metal hip joint prostheses from January 1, 1984 to the present, and identify all risks included in these reports.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your reclassification petition application can be completed and presented to the Orthopedic and Rehabilitation Devices Advisory Committee. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(e) of the Federal Food, Drug, and Cosmetic Act for the purposes of reclassifying these devices. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

This letter reflects the current progress of our review of your application. Please be advised that further substantive review of your application or any response to this letter may result in additional deficiencies.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period.

FDA will consider this reclassification petition to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a reclassification petition amendment. You may, however, amend the reclassification petition within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested

information will be submitted. If you do not amend reclassification petition within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the reclassification petition and will be assigned a new docket number. Under these circumstances, any resubmission will be given a new reclassification petition number and will follow Section 513 of the Food, Drug, and Cosmetic Act.

You may amend the reclassification petition to provide the above requested information (7 Copies for FDA review – 20 Copies for Advisory Panel review), voluntarily withdraw the reclassification petition(3 copies), direct CDRH to complete processing the reclassification petition without the submission of additional information (3 copies) or request an extension. The required copies of the amended reclassification petition should include the FDA reference number for this reclassification petition and should be submitted to the following address:

Reclassification Petition
Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests, CDRH will schedule an advisory panel meeting at which your reclassification petition will be reviewed. You will be notified of the location and date of this meeting. Any additional information to be included in your reclassification petition should be submitted in the form of a reclassification petition amendment and be received by FDA at least 10 weeks in advance of the scheduled advisory panel meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 8 weeks in advance of a scheduled advisory panel meeting will not be considered or reviewed at the meeting and may delay consideration of your reclassification petition until a subsequent advisory panel meeting.

If you have any questions concerning this deficiency letter, please contact Mr. Glenn Stiegman at (301) 594-2036 ext. 166.

Sincerely yours,

Kimber Richter

Kimber C. Richter, MD
Deputy Director for Clinical and
Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure: "General ORDB Outline for Clinical Data Presentation in Premarket Notifications (510(k)) Submissions, Investigational Device Exemptions (IDE) Annual Reports, or Premarket Approval (PMA) Applications" dated June 1991.

General ORDB Outline for Clinical Data Presentations in Premarket Notifications (510(k)) Submissions, Investigational Device Exemptions (IDE) Annual Reports, or Premarket Approval (PMA) Applications
June 1991

The tables provided to demonstrate the preparation of the minimum required content for IDE annual reports, IDE final reports and PMA reports utilize certain terms. These terms, as they are associated with specific tables, are defined below. The example provided is for a clinical study involving 100 implantations with less than 2 years follow-up due on any implant.

Table I. Definitions

Theoretical Follow-up:

The theoretical follow-up is the number of implants that would have been examined if all patients had returned on the exact anniversary of their respective surgery dates. The theoretical follow-up is determined by selecting a date of database closure. This is the date the data base is closed to the addition of information. Having selected a date of database closure one can determine the theoretical follow up. For each implant in the investigation one determines the time difference between implantation and the date of closure. Knowing this one can determine which of the scheduled follow-up examinations the patient should have attended. This process is repeated for each implant enrolled in the investigation. The number of implants that should have been examined at each scheduled follow-up visit is summed and this number is the theoretical follow-up.

In order to permit data gathered from the patients up to the date of database closure to be entered into the report the common practice is to select a date of closure in the recent past, i.e., within a couple of weeks prior to the date of report preparation. All data gather from patients examined up to and including the date of database closure are entered into the report. Patient data arriving in the hands of a sponsor after the date of database closure that was recorded from a patient examination that took place on or prior to the date of closure is entered into the report.

Deaths:

The time course of deaths is the arrangement, according to scheduled follow-up visit, of the deaths that have taken place in the course of an investigation. In the example a patient died some time between release for the hospital and the 3 month follow-up visit. This patient is recorded as having died at the 3 month follow-up visit because he was not examined for his 3 month follow-up. Some time between the each of their individually scheduled 6 month and 12 month follow-ups 3 different patients died. These 3 patients are recorded as deaths at the 12 month follow-up visit. These patients are recorded at 12 months because no 12 months examination was gathered or possible.

Revisions:

Revisions are handled the same as deaths. In the example a patient was revised at or prior to the immediate post-op examination. This revision is reported under the immediate post-op follow-up visit. Some time between their immediate post-op examinations and their individually scheduled 3 month follow-ups 2 additional patients had revisions. These 2 revisions are reported under the 3 month follow-up because they were examined immediately post-op but were not examined at 3 months. An additional patient was revised after making his 3 month follow-up but before a 6 month follow-up visit was due. Because there could be no 6 month follow-up this patient is reported as revised under the 6 month interval.

Complications:

The time course of complications follows the same logic as the Table I concepts. Each complication that has been reported during the investigation is identified by listing all complications down the left hand side of the page. Across the top of the page are the scheduled follow-up visits. If a complication took place at or before the immediate post-op examination, as myocardial infarction in the example, the number of occurrences is reported under the immediate post-op heading. Again from the example, some time between their 3 month follow-up visits and their 6 month follow-up visits 2 additional patient experienced MIs. These patients are reported under the 6 month visit because they had already had their 3 month examination but had not had their 6 month examination before the complication occurred.

Summary of Clinical Findings:

In orthopedics most evaluation methods involve a category of data known as ordinal data. Because of the nature of ordinal data such concepts as means and standard deviations are of limited usefulness and may even be misrepresentations of the information. When an evaluation method such as a Harris Hip Score is used the data must be presented as the number of implants with each rating. In the example a typical orthopedic clinical evaluation system is presented. Under A Total Score are the number of implants that fall into the excellent, good, fair and poor categories for each follow-up time point. Under B Pain Score are the number of implants that fall into each of scoring system's pain categories. Under C Function Score the number of implants that fall into each of the function categories.

Demographics:

A description of the patient population is always necessary. The basic elements are age (number of patients, the mean age ± the standard deviation of the age), the distribution of implants among diagnoses. Here all of the diagnoses recorded in the investigation are listed. With each diagnosis is listed the number of implants that have that diagnosis. Gender should be self explanatory.

Reiterations of the above forms of information describing specific subsets of clinical data may be required on occasions and in specific cases other information not identified above may be required.

CLINICAL REPORT TABLES FOR THE GENERAL CASE

I. PATIENT ACCOUNTING

	FOLLOW-UP TIME POINTS			
	IMMEDIATE POST-OP	3 MONTHS	6 MONTHS	12 MONTHS
Theoretical Follow-up	100	85	50	30
Deaths	0	1	0	3
Revisions	1	2	1	2

II. COMPLICATIONS

	FOLLOW-UP TIME POINTS			
	IMMEDIATE POST-OP	3 MONTHS	6 MONTHS	12 MONTHS
Systemic Complications				
Myocardial Infarction	3	0	2	1
Pulmonary Emboli	5	3	2	0
Etc.	2	5	3	7
Etc.	4	1	4	2
Etc.	0	1	1	0
Operative Site Complications				
Infection	2	4	0	3
Wound Dehiscence	3	0	0	0
Etc.	0	1	2	1
Etc.	0	2	4	2
Etc.	1	0	1	1

III. SUMMARY OF CLINICAL AND RADIOGRAPHIC FINDINGS

A. TOTAL SCORE

NUMBERS OF JOINTS WITH IDENTIFIED RATING AT FOLLOW-UP TIME POINT

SCORE RATING	IMMEDIATE POST-OP	3 MONTH	6 MONTH	12 MONTH
EXCELLENT (91-100)	10	25	25	15
GOOD (81-90)	25	35	10	0
FAIR (71-80)	50	5	3	3
POOR (<71)	15	5	1	1

B. PAIN SCORE

NONE (40-45)	0	5	15	10
MILD (30-39)	2	15	15	5
MODERATE (20-29)	15	40	4	2
SEVERE (10-19) 60	5	4	0	
DISABLED (0-9) 23	5	1	1	

C. FUNCTION SCORE

NORMAL (40-45)	5	7	17	12
MILD DISFNT (30-39)	15	17	17	6
MOD. DISFNT (20-29)	65	30	5	0
SEVERE (10-19) 10	16	0	1	
DISABLED (0-9) 5	0	0	0	

D. ETC.

IV. DEMOGRAPHICS

A. AGE
- NUMBER OF PATIENTS
- MEAN ± STANDARD DEVIATION
- RANGE
- BY DECADE OF LIFE

B. DIAGNOSIS

NONINFLAMMATORY DEGENERATIVE JOINT DISEASE	70 JOINTS	70 PATIENTS
OSTEOARTHRITIS	55 JOINTS	55 PATIENTS
AVASCULAR NECROSIS	10 JOINTS	10 PATIENTS
POST TRAUMATIC ARTHRITIS	5 JOINTS	5 PATIENTS
RHEUMATOID ARTHRITIS	15 JOINTS	13 PATIENTS
CONGENITAL DISORDER	5 JOINTS	5 PATIENTS
REVISION OF PREVIOUS PROSTHESIS	10 JOINTS	10 PATIENTS

C. GENDER

MALES	65 JOINTS	67 PATIENTS
FEMALE	33 JOINTS	30 PATIENTS